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Please find below a communication from the EXAMINER in charge of this application.

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Paper No. 47

Serial Number: 08/192,800
Filing Date: 2/7/94
Appellant(s): Sudoh et al.

Andrew Fortney
For Appellants

EXAMINER'S ANSWER

This is in response to appellants brief on appeal filed 11/13/95.

(1) *Status of claims.*

The statement of the status of claims contained in the brief is correct.

(2) *Status of Amendments After Final.*

Appellants' statement of the status of amendments after final rejection contained in the brief is correct.

(3) *Summary of invention.*

The summary of invention contained in the brief is correct.

(4) *Issues.*

The appellants' statement of the issues in the brief is correct.

(5) *Grouping of claims.*

The rejection of claims 2-7 and 10-35 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.162(c)(5).

(6) *Claims appealed.*

The copy of the appealed claims contained in the Appendix to the brief is correct.

(7) *Prior Art of record.*

Sudoh et al. (R), Nature, 332, 78-81, March 3, 1988.

Sudoh et al. (T), Biochem. Biophys. Res. Comm., 155:726-732, Sept. 15, 1988.

Oikawa et al., Biochem. Biophys. Res. Comm., 132:892-899, 1985.

Vlasuk et al., Biochem. Biophys. Res. Comm., 136:396-403, 1986.

Maniatis et al., Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, pages 226-228, 412-413, 422, and 518, 1982.

Maekawa et al., Biochem. Biophys. Res. Comm., 157:410-416, Nov. 30, 1988.

Sudoh et al. (AR), Biochem. Biophys. Res. Comm., 159:1427-1433, March 31, 1989.

(8) *New prior art.*

No new prior art has been applied in this examiner's answer.

(9) *Grounds of rejection.*

The following ground(s) of rejection are applicable to the appealed claims.

Claims 2-7 and 10-35 stand finally rejected under 35 U.S.C. § 103 as being unpatentable over Maekawa et al. in view of Maniatis et al. and further in view of Sudoh et al. (R) and Sudoh et al. (T), and Oikawa et al. and Vlasuk et al.

Sudoh et al (R) teach the amino acid sequence of porcine brain natriuretic peptide (pBNP) isolated from brain and show in Fig.2 on page 80 a high degree of homology between the amino acid sequence of pBNP and human atrial natriuretic peptide (hANP).

Sudoh et al. teach pBNP of two forms BNP (26 amino acids in length) and BNP-32 (32 amino acids in length).

Oikawa et al. teach the isolation of the dog and rabbit cDNA encoding ANP using the human ANP cDNA.

Vlasuk et al. teach the isolation of the bovine cDNA encoding ANP using the human ANP cDNA.

Maniatis et al. teaches the general techniques for isolating and cloning cDNAs.

Maekawa et al. teach the isolation of the pBNP cDNA by constructing oligo probes using the amino acid sequence for pBNP.

Sudoh et al. (AR) teach the isolation of the human BNP (hBNP) cDNA using the porcine BNP cDNA. Note that Sudoh et al. (AR) is cited as of interest only. This reference has not been included as reference in instant section 103 rejection.

The difference between what is taught by the prior art and what is claimed is the isolation of the cDNA encoding hBNP.

Maekawa use the pBNP amino acid sequences 2-6 ((Pro-Lys-Thr-Met-Arg) following the pBNP-32 amino acid sequence of Sudoh (T)) and 19-23 ((Gly-Cys-Asn-Val-Leu) following the pBNP amino acid sequence of Sudoh (R)) to construct a set of successful probes to isolate the pBNP cDNA.

With the porcine cDNA for BNP, one of ordinary skill would have been motivated to isolate the corresponding human cDNA for the use in recombinant production of the human protein as a therapeutic. Two facts from the prior art provide a reasonable expectation that the pBNP cDNA would have successfully been used as a probe to isolate the human BNP (hBNP) cDNA from a brain library: 1) Sudoh (R) show in figure 2 and Sudoh (T) show in fig. 5 that pBNP and hANP are highly homologous and 2) Oikawa et al. and Vlasuk et al. teach that the cDNAs of ANP can be used to isolate the cDNAs of other species (specifically the human ANP cDNA was used to successfully isolated the dog, rabbit and bovine cDNAs). Thus given that: 1) BNP and ANP are highly homologous and closely related evolutionarily, and 2) that the homologous ANP cDNAs can be isolated across species in mammalia, one of ordinary skill would have reasonably expected that BNP cDNAs would have been found across mammalia as for ANP cDNAs, in nervous tissue such as brain just as ANPs are found in atrial or cardiac tissue across mammalia, and that one BNP cDNA would have been reasonably expected to isolate BNP cDNAs across mammalia as was the case for the isolation of ANP cDNAs across mammalia.

Appellants attention is directed to Sudoh et al. (AR). While not cited as part of the instant rejection, it is, however, interesting to note that this reference teaches the routine isolation

of the human BNP cDNA using the porcine BNP cDNA.

Note further that claims 30-35 are directed to a method of producing a cDNA which is essentially identical to the same method as taught by Maniatis et al. (see pages 227-228, Differential Hybridization). No evidence or arguments have been presented which would indicate that the instant hBNP cDNA possesses or possessed unique properties with respect to the prior art method of cDNA isolation as disclosed by Maniatis et al. Therefore, one would have fully expected the prior art process to be completely applicable to the instant invention.

(10) *New ground of rejection.*

This Examiner's Answer does not contain any new ground of rejection.

(11) *Response to argument.*

Essentially it is appellants position that Seilhamer et al. (U.S. Patent No. 5,114,923) teaches away from the instant invention since Seilhamer teaches that they failed to isolate the hBNP cDNA utilizing the Seilhamer pBNP cDNA as disclosed. However, this outcome is not surprising since as per Experiment 5 found in col. 23, Seilhamer used the putative cDNA as shown in Figure 1 which contained an unprocessed intron, and thus not a true and/or a complete cDNA. Even though this putative cDNA was used to screen a human genomic library, which contains introns, the appropriate probe to use for this screening would have been the complete genomic pBNP gene and not a incomplete cDNA since the expectation would have been that the genomic sequence would contain other introns or other intervening sequences. Therefore, it is not surprising that Seilhamer failed to isolate the hBNP genomic clone. This being the expectation based on the experiment in Example 5, Seilhamer does not teach away from using the completely processed porcine BNP gene (a true or complete cDNA devoid of introns or intervening sequences) as a probe, this being a routine method of cDNA isolation (as per Maniatis for

example), and as was done for the evolutionarily related ANP cDNAs.

Appellants argue further that the examiner has made a leap of faith not consistent with a section 103 rejection. Essentially, it appears to be appellants position that the example cited of the art analogous and highly related evolutionarily, in terms of protein structure (amino acid sequence and thus gene sequence as well) and function, ANPs and the isolation across mammalia of their cDNAs using a cDNA probe provides no assurance of doing the same for BNP.

This is not agreed with. As argued above in the section 103 rejection, ANPs and BNPs were taught by the prior art cited above (even Seilhamer) to be evolutionarily to be highly related proteins in terms of structure and function, with BNPs very likely to have evolved from ANPs. One of ordinary skill could not help but see this association and realize that based on the extremely high degree of similarity in terms of both structure and function between ANPs and BNPs, that BNP genes are very likely to behave similarly as for ANPs (including cDNA isolation). Thus, the fact that an ANP cDNA successfully isolated ANP cDNAs across mammalia, one is provided not only with an art analogous example for the BNP situation across mammalia, but an example of a gene which is highly related based on evolution. One could not cite a closer example (ANPs) or situation for BNPs. It would seem that appellants would have the Examiner cite an explicit teaching that a BNP cDNA would have been successful. However the standard applied to section 103 rejections is a reasonable expectation of success based on what the prior art would have suggested to one of ordinary skill. Explicit teachings are not required. The Court of Customs and Patent Appeals found in In re Keller, Terry, and Davies 208 USPQ 871, 881 (CCPA, 1981):

> [t]o justify combining reference teachings in support of a rejection it is not necessary that a device shown in one reference can be

physically inserted into the device shown in the other.... The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

John L. LeGUYADER
January 16, 1996

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